(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 April 2003 (03.04.2003)

PCT

(10) International Publication Number
WO 03/026616 A1

(51) International Patent Classification[7]: A61K 9/00, 9/20, 9/28

(21) International Application Number: PCT/US02/31164

(22) International Filing Date:
28 September 2002 (28.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

09/966,939	28 September 2001 (28.09.2001)	US
09/966,509	28 September 2001 (28.09.2001)	US
09/966,497	28 September 2001 (28.09.2001)	US
09/967,414	28 September 2001 (28.09.2001)	US
09/966,450	28 September 2001 (28.09.2001)	US

(71) Applicant *(for all designated States except US)*: **MCNEIL-PPC, INC.** [US/US]; Grandview Road, Skillman, NJ 08558 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BUNICK, Frank, J.** [US/US]; 750 E. Cherry Road, Quakertown, PA 18951 (US). **LABELLA, Gus, B.** [US/US]; 176 Stine Drive, Collegeville, PA 19426 (US). **SOWDEN, Harry, S.** [US/US]; 209 Woods Road, Glenside, PA 19038 (US).

(74) Agents: **JOHNSON, Philip, S.** et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08903 (US).

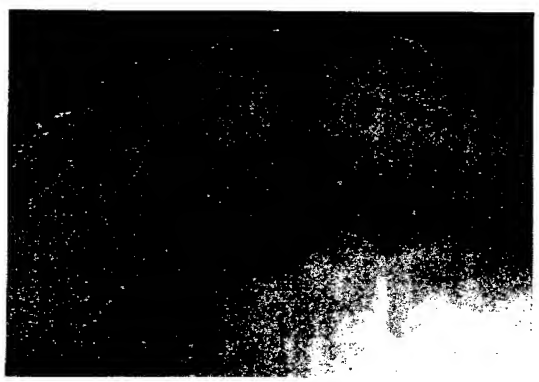
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

(54) Title: EDIBLE COMPOSITION AND DOSAGE FORM COMPRISING AN EDIBLE SHELL



(57) Abstract: An edible product comprises at least about 50 % by weight of a crystallizable carbohydrate based upon the weight of the product, wherein at least about 90 % by weight of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less, the product has a moisture content of not more than about 5 % by weight loss on drying, at least about 30 % of the cross-sectional area of the product is non-striated, and the edible product has a cross-sectional area in the range of about 1 to 900 sq. mm. A dosage form comprises at least one active ingredient and the edible product, or at least one active ingredient, a shell comprising the edible product, and a substrate such as a core. The shell or core or both may contain an active ingredient such as a pharmaceutically active ingredient.

WO 03/026616 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

EDIBLE COMPOSITION AND DOSAGE FORM COMPRISING AN EDIBLE SHELL

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] This invention relates to an edible product which may be used as a dosage form per se, or as a component of a dosage form, for example comprising a shell, such as pharmaceutical compositions comprising a shell. Dosage forms of this invention comprise at least one active ingredient and the edible product itself, or may comprise a shell comprising the edible product and a substrate or core which is surrounded at least in part by the shell.

[0002] Background Information

[0003] Sugar-based coatings are well known in the confectionery industry, and are used for example to encapsulate cores comprising jellies, chocolate, fondants, and the like. Conventional methods for applying sugar based coatings include hard-panning, and soft panning techniques which are described in detail in e.g., Lachman, L., Lieberman, H. A., and Kanig, J.L.: The Theory and Practice of Industrial Pharmacy, 2nd ed., Lea & Febiger, Philadelphia, 1976, Chapter 12, pages 359-368; and W.P.P. Edwards: The Science of Sugar Confectionery, 1st ed., The Royal Society of Chemistry, London, 2000, Chapter 8, pages 95-100; and B. W. Minifie, Chocolate, Cocoa, and Confectionery: Science and Technology, AVI Publishing Company, Inc. January 1980, Chapter 19, pages 608-613. Shells produced by hard-panning comprise crystals of relatively small particle size, e.g. about 2 to about 20 microns, and relatively narrow particle size distribution. Hard panned coatings are applied in several layers, which can generally be viewed in a cross-section utilizing a light microscope. Shells prepared by soft-panning have a wider distribution of crystal size, with at least a portion of the crystals having a size of at least 100 microns or more. Sugar-coated pharmaceutical tablets are well known, and representative compositions and methods for

manufacture are disclosed, for example, in Ceschel, G.C. et. al., "Sugar Coating of Tablets", *Bollettino Chimico Farmaceutico*, vol. 119, (Mar), pages 127-134, 1980; and Schneider, H.; Speiser, P., "Contribution to Sugar Coating Tablets", *Pharmaceutica Acta Helvetiae*, vol. 43, (Jul), pages 394-410; and Porter, S.C., "Tablet Coating. Part 1", *Drug Cosmet. Ind.*, vol. 128, (May), 1981, pages 46-53 and 86-93. These dosage forms comprise a glossy hard shell, which imparts protection, physical and chemical stability, visual elegance, and a sweet taste to the dosage form. Conventional methods for applying sugar-based coatings are relatively time consuming, resulting in high processing costs.

[0004] Accordingly, it is one object of this invention to provide a method of making an edible shell for a dosage form which may be performed rapidly with low processing costs.

[0005] It is another object of this invention to provide a method of making a dosage form having such an edible shell.

[0006] It is another object of this invention to provide an edible product which may be applied to a substrate such as a core.

[0007] It is another object of this invention to provide a dosage form comprising the edible shell of this invention.

[0008] It is another object of this invention to provide a dosage form comprising the edible product of this invention.

[0009] Other objects, features and advantages of this invention will be apparent to those skilled in the art from the detailed description of the invention provided herein.

SUMMARY OF THE INVENTION

[0010] The edible product of this invention comprises at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the product, wherein at least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average

particle size of about 100 microns or less, the product has a moisture content of not more than about 5% by weight loss on drying, at least about 30% of the cross-sectional area of the product is non-striated, and the product has a cross-sectional area in the range of about 1 to 900 sq. mm.

[0011] In another embodiment, the product comprises about 60% of a crystallizable carbohydrate.

[0012] In another embodiment, the product comprises about 75% of a crystallizable carbohydrate.

[0013] In another embodiment, the crystals have an average particle size of less than about 50 microns.

[0014] In another embodiment, the product has a moisture content of not more than about 3% loss on drying.

[0015] In another embodiment, the product has a moisture content of not more than about 1% loss on drying.

[0016] In another embodiment at least about 50% of the cross-sectional area of the product is non-striated.

[0017] In another embodiment at least about 80% of the cross-sectional area is non-striated.

[0018] In another embodiment, the product comprises at least one active ingredient.

[0019]

[0020] In one embodiment, the edible product of this invention may be prepared by a method comprising: (a) injecting a flowable crystallizable carbohydrate into a mold cavity;

(b) hardening the flowable crystallizable carbohydrate into an edible product in the mold cavity; and (c) removing the edible product from the mold cavity.

[0021] The dosage form of this invention comprises at least one active ingredient and an edible shell residing on at least a portion of a substrate, wherein the shell comprises at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the shell, at least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less, the shell has a moisture content of not more than about 5% by weight loss on drying, at least about 30% of the cross-sectional area of the shell is non-striated, and the dosage form has a cross-sectional area in the range of about 1 to 900 sq. mm.

[0022] In another embodiment, the shell comprises a first portion and a second portion which are joined at an interface.

[0023] In another embodiment, the first and second shell portions are visually distinct.

[0024] In another embodiment, the substrate comprises an active ingredient.

[0025] In another embodiment, the substrate is a core, and the edible shell surrounds the core.

[0026] In another embodiment, the shell comprises an active ingredient.

[0027] In another embodiment, the core comprises an active ingredient.

[0028] In another embodiment, the shell and the core each comprise an active ingredient.

[0029] In another embodiment, the active ingredient is capable of dissolution upon contacting of the dosage form with a liquid medium, and dissolution of the active ingredient meets USP specifications for immediate release tablets containing the active ingredient.

[0030] In one embodiment, the dosage form of this invention may be prepared by a method comprising: (a) providing a substrate; (b) surrounding at least a portion of the substrate with an edible shell, wherein the shell comprises at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the shell, at least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less, the shell has a moisture content of not more than about 5% by weight loss on drying, at least about 30% of the cross-sectional area of the shell is non-striated, and the dosage form has a cross-sectional area in the range of about 1 to 900 sq. mm; and (c) providing at least one active ingredient in the substrate or the shell or a combination thereof.

[0031] In another embodiment, the dosage form of this invention may be prepared by a method comprising: (a) injecting a heated, flowable, crystallizable carbohydrate into a mold cavity containing a substrate such that the flowable crystallizable carbohydrate surrounds a first portion of the substrate within the mold cavity; (c) changing the temperature of the mold cavity to induce thermal shock crystallization of the flowable crystallizable carbohydrate surrounding a first portion of the substrate; (d) opening the mold cavity and rotating the portion of the mold containing the substrate to expose a second portion of the substrate; (e) closing the mold cavity; (f) injecting heated, flowable, crystallizable carbohydrate into the mold cavity such that the flowable crystallizable carbohydrate surrounds the second portion of the substrate within the mold cavity; (g) rapidly changing the temperature of the mold cavity to induce thermal shock crystallization of the flowable crystallizable carbohydrate surrounding the second portion of the substrate; and (h) removing the substrate from the mold cavity.

[0032] In another embodiment, the dosage form of this invention comprises at least one active ingredient and at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the dosage form, wherein at least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less, the dosage form has a moisture content of not more than about 5% by weight loss on drying, at least about 30% of the cross-sectional area of the dosage form is non-striated, and the dosage form has a cross-sectional area in the range of about 1 to 900 sq. mm.

[0033] In another embodiment, the dosage form comprises about 60% of a crystallizable carbohydrate.

[0034] In another embodiment, the dosage form comprises about 75% of a crystallizable carbohydrate.

[0035] In another embodiment, the crystals have an average particle size of less than about 50 microns.

[0036] In another embodiment, the dosage form has a moisture content of not more than about 3% loss on drying.

[0037] In another embodiment, the dosage form has a moisture content of not more than about 1% loss on drying.

[0038] In another embodiment, at least about 50% of the cross-sectional area of the dosage form is non-striated.

[0039] In another embodiment, at least about 80% of the cross-sectional area of the dosage form is non-striated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] Figures 1A and 1B depict cross-sectional micrographs of prior art pan coated sugar shells.

[0041] Figures 2A and 2B depict cross-sectional and side views, respectively, of the dosage form of Example 1.

DETAILED DESCRIPTION OF THE INVENTION

[0042] As used herein, the term "dosage form" applies to any solid object, semi-solid, or liquid composition designed to contain a specific pre-determined amount (i.e. dose) of a certain ingredient, for example an active ingredient as defined below. Suitable dosage forms may be pharmaceutical drug delivery systems, including those for oral administration, buccal administration; or compositions for delivering minerals, vitamins and other nutraceuticals, oral care agents, flavorants, and the like. Preferably the dosage forms of the present invention are considered to be solid, however they may contain liquid or semi-solid components. In a particularly preferred embodiment, the dosage form is an orally administered system for delivering a pharmaceutical active ingredient to the gastro-intestinal tract of a human.

[0043] Suitable active ingredients for use in this invention include for example pharmaceuticals, minerals, vitamins and other nutraceuticals, oral care agents, flavorants and mixtures thereof. Suitable pharmaceuticals include analgesics, anti-inflammatory agents, antiarthritics, anesthetics, antihistamines, antitussives, antibiotics, anti-infective agents, antivirals, anticoagulants, antidepressants, antidiabetic agents, antiemetics, antiflatulents, antifungals, antispasmodics, appetite suppressants, bronchodilators, cardiovascular agents, central nervous system agents, central nervous system stimulants, decongestants, diuretics, expectorants, gastrointestinal agents, migraine preparations, motion sickness products,

mucolytics, muscle relaxants, osteoporosis preparations, polydimethylsiloxanes, respiratory agents, sleep-aids, urinary tract agents and mixtures thereof.

[0044] Suitable oral care agents include breath fresheners, tooth whiteners, antimicrobial agents, tooth mineralizers, tooth decay inhibitors, topical anesthetics, mucoprotectants, and the like.

[0045] Suitable flavorants include menthol, peppermint, mint flavors, fruit flavors, chocolate, vanilla, bubblegum flavors, coffee flavors, liqueur flavors and combinations and the like.

[0046] Examples of suitable gastrointestinal agents include antacids such as calcium carbonate, magnesium hydroxide, magnesium oxide, magnesium carbonate, aluminum hydroxide, sodium bicarbonate, dihydroxyaluminum sodium carbonate; stimulant laxatives, such as bisacodyl, cascara sagrada, danthron, senna, phenolphthalein, aloe, castor oil, ricinoleic acid, and dehydrocholic acid, and mixtures thereof; H2 receptor antagonists, such as famotadine, ranitidine, cimetadine, nizatidine; proton pump inhibitors such as omeprazole or lansoprazole; gastrointestinal cytoprotectives, such as sucraflate and misoprostol; gastrointestinal prokinetics, such as prucalopride, antibiotics for H. pylori, such as clarithromycin, amoxicillin, tetracycline, and metronidazole; antidiarrheals, such as diphenoxylate and loperamide; glycopyrrolate; antiemetics, such as ondansetron, analgesics, such as mesalamine.

[0047] In one embodiment of the invention, the active agent may be selected from bisacodyl, famotadine, ranitidine, cimetidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, antacids, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0048] In another embodiment of the invention, the active agent may be selected from acetaminophen, acetyl salicylic acid, ibuprofen, naproxen, ketoprofen, flurbiprofen, diclofenac, cyclobenzaprine, meloxicam, rofecoxib, celecoxib, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0049] In another embodiment of the invention, the active agent may be selected from pseudoephedrine, phenylpropanolamine, chlorpheniramine, dextromethorphan, diphenhydramine, astemizole, terfenadine, fexofenadine, loratadine, desloratadine, cetirizine, mixtures thereof and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0050] Examples of suitable polydimethylsiloxanes, which include, but are not limited to dimethicone and simethicone, are those disclosed in United States Patent Nos. 4,906,478, 5,275,822, and 6,103,260, the contents of each is expressly incorporated herein by reference. As used herein, the term "simethicone" refers to the broader class of polydimethylsiloxanes, including but not limited to simethicone and dimethicone.

[0051] The active ingredient or ingredients are present in the dosage form in a therapeutically effective amount, which is an amount that produces the desired therapeutic response upon oral administration and can be readily determined by one skilled in the art. In determining such amounts, the particular active ingredient being administered, the bioavailability characteristics of the active ingredient, the dose regime, the age and weight of the patient, and other factors must be considered, as known in the art. In one embodiment, the core comprises at least about 85 weight percent of the active ingredient.

[0052] If the active ingredient has an objectionable taste, and the dosage form is intended to be chewed or disintegrated in the mouth prior to swallowing, the active ingredient may be coated with a taste masking coating, as known in the art. Examples of suitable taste masking coatings are described in U.S. Patent No. 4,851,226, U.S. Patent No. 5,075,114, and

U.S. Patent No. 5,489,436. Commercially available taste masked active ingredients may also be employed. For example, acetaminophen particles which are encapsulated with ethylcellulose or other polymers by a coaccervation process may be used in the present invention. Coaccervation-encapsulated acetaminophen may be purchased commercially from Eurand America, Inc. (Vandalia, Ohio) or from Circa Inc. (Dayton, Ohio).

[0053] In embodiments wherein the dosage form comprises a compressed core, suitable excipients for compression include fillers, binders, disintegrants, lubricants, glidants, and the like.

[0054] Suitable fillers include water-soluble compressible carbohydrates such as sugars, which include dextrose, sucrose, maltose, and lactose, sugar-alcohols, which include mannitol, sorbitol, maltitol, xylitol, starch hydrolysates, which include dextrins, and maltodextrins, and the like, water insoluble plasticly deforming materials such as microcrystalline cellulose or other cellulosic derivatives, water-insoluble brittle fracture materials such as dicalcium phosphate, tricalcium phosphate and the like and mixtures thereof.

[0055] Suitable binders include dry binders such as polyvinyl pyrrolidone, hydroxypropylmethylcellulose, and the like; wet binders such as water-soluble polymers, including hydrocolloids such as alginates, agar, guar gum, locust bean, carrageenan, tara, gum arabic, tragacanth, pectin, xanthan, gellan, maltodextrin, galactomannan, pusstulan, laminarin, scleroglucan, gum arabic, inulin, pectin, whelan, rhamsan, zooglan, methylan, chitin, cyclodextrin, chitosan, polyvinyl pyrrolidone, cellulosics, starches, and the like; and derivatives and mixtures thereof.

[0056] Suitable disintegrants include sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, starches, microcrystalline cellulose, and the like.

[0057] Suitable lubricants include long chain fatty acids and their salts, such as magnesium stearate and stearic acid, talc, and waxes.

[0058] Suitable glidants include colloidal silicon dioxide, and the like.

[0059] The dosage form of the invention may also incorporate pharmaceutically acceptable adjuvants, including, for example, preservatives, high intensity sweeteners such as aspartame, acesulfame potassium, sucralose, and saccharin; flavors, antioxidants, surfactants, and coloring agents.

[0060] The active ingredient or ingredients are preferably capable of dissolution upon contact with a fluid such as water, gastric fluid, intestinal fluid or the like. In a preferred embodiment the dissolution characteristics of the active ingredient meets USP specifications for immediate release tablets containing the active ingredient. In embodiments in which it is desired for the active ingredient to be absorbed into the systemic circulation of an animal, the active ingredient or ingredients are preferably capable of dissolution upon contact with a fluid such as water, stomach acid, intestinal fluid or the like. In one embodiment, the dissolution characteristics of the active ingredient meets USP specifications for immediate release tablets containing the active ingredient. For example, for acetaminophen tablets, USP 24 specifies that in pH 5.8 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the acetaminophen contained in the dosage form is released therefrom within 30 minutes after dosing, and for ibuprofen tablets, USP 24 specifies that in pH 7.2 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the ibuprofen contained in the dosage form is released therefrom within 60 minutes after dosing. See USP 24, 2000 Version, 19 –

20 and 856 (1999). In another embodiment, the dissolution characteristics of the active ingredient are modified: e.g. controlled, sustained, extended, retarded, prolonged, delayed and the like.

[0061] The active ingredient or ingredients may be present in the dosage form in any form. For example, the active ingredient may be dispersed at the molecular level, e.g. melted or dissolved, within the dosage form, or may be in the form of particles, which in turn may be coated or uncoated. If the active ingredient is in form of particles , the particles (whether coated or uncoated) typically have an average particle size of about 1-2000 microns. In one preferred embodiment, such particles are crystals having an average particle size of about 1-300 microns. In another preferred embodiment, the particles are granules or pellets having an average particle size of about 50-2000 microns, preferably about 50-1000 microns, most preferably about 100-800 microns.

[0062] The edible product of this invention comprises at least about 50% by weight, more preferably at least about 60% by weight, most preferably at least about 75% by weight of a crystallizable carbohydrate. Suitable crystallizable carbohydrates include, for example the monosaccharides and the oligosaccharides. Of the monosaccharides, the aldohexoses e.g., the D and L isomers of allose, altrose, glucose, mannose, gulose, idose, galactose, talose, and the ketohexoses e.g., the D and L isomers of fructose and sorbose along with their hydrogenated analogs e.g., glucitol (sorbitol), and mannitol are preferred. Of the oligosaccharides, the 1,2-disaccharides sucrose and trehalose, the 1,4-disaccharides maltose, lactose, and cellobiose, and the 1,6-disaccharides gentiobiose and melibiose, as well as the trisaccharide raffinose are preferred along with the isomerized form of sucrose known as isomaltulose and its hydrogenated analog isomalt. Other hydrogenated forms of reducing disaccharides (such as maltose and lactose), for example maltitol and lactitol are also preferred. Additionally, the hydrogenated forms of the aldopentoses e.g., D and L ribose,

arabinose, xylose, and lyxose and the hydrogenated forms of the aldotetroses e.g., D and L erythrose and threose are preferred and are exemplified by xylitol and erythritol, respectively.

[0063] In one embodiment the crystallizable carbohydrate may be selected from sucrose, sorbitol, mannitol, xylitol, erythritol, maltitol, lactitol, and derivatives and mixtures thereof. In one embodiment, the crystallizable carbohydrate is a fondant grade sugar. In another embodiment, the crystallizable carbohydrate is a sugar glass, such as for example the product obtained by cooling a cooked sugar and corn syrup mixture.

[0064] The crystallizable carbohydrate may have any suitable particle size. Preferably, the crystallizable carbohydrate will have a particle size ranging from about 2 to about 1000 microns. In one embodiment wherein the crystallizable carbohydrate is fondant grade sugar, the particle size of the crystallizable carbohydrate is preferably from about 2 to about 35 microns. In another embodiment wherein the crystallizable carbohydrate is heated to a molten state, the crystalizable carbohydrate may have a particle size from about 2 to about 1000 microns, or about 1000 microns to about 5000 microns.

[0065] Preferably, at least about 90% by weight of the crystallizable carbohydrate is in the crystalline form, and has an average particle size of about 100 microns or less, typically about 50 microns or less.

[0066] The moisture content of the edible product of the present invention is such that there is typically not more than about 5% by weight loss on drying, preferably, not more than about 3%, most preferably not more than about 1% by weight loss on drying. Loss on drying (L.O.D.) may be measured by the following method: a sample (typically about 1 to about 10 grams) of the edible product is prepared by subdividing it into small pieces of about 1 to about 2 square millimeters in size, or ground to a coarse powder. A known quantity of the prepared sample is placed into a tared aluminum weigh boat and dried in a desiccator

containing anhydrous calcium sulfate or other suitable drying agent until a constant weight is achieved. The difference in weight after drying from the original sample is expressed as percent moisture. Alternatively, the USP Method <731> Loss on Drying may be used.

[0067] The costly and lengthy prior art method for sugar coating tablets and pharmaceutical dosage forms by panning techniques gives rise to a characteristic striated pattern, which is visible in the cross section of such dosage forms or their sugar shells (see for example Figure 1A and 1B). These characteristic striations are indicative of the panning process consisting of multiple repetitions of the steps consisting of a.) applications of sugar syrup followed by b.) warm air drying, to a tumbling bed of dosage forms in a revolving coating pan such that numerous layers of finely crystallized sugar are built up as each application of sugar crystallizes upon drying to form a layer. The thickness of an individual layer is typically in the range of about 0.01 mm to about 0.013 mm.

[0068] In contrast, the edible product of the present invention may advantageously be applied as sugar shell to a substrate directly by a molding process, yielding a uniform and homogeneous layer in 5 minutes or less, e.g. 60 seconds or less, or 30 seconds or less, or 10 seconds or less, and in certain embodiments, say 1 second or less. As such, at least about 30%, preferably at least about 50%, most preferably at least about 80% of the cross-sectional area of the edible product of the present invention is non-striated. As used herein, "non-striated" means homogeneous with respect to appearance, and with respect to the internal structure of the sugar matrix of the edible product when viewed under any magnification and lighting conditions. For example a cross-section of the product is free of striations, and uniform with respect to refractive properties when observed utilizing a light microscope at a magnification of about 50 to about 400 times.

[0069] The edible product or edible shell of the present invention has a cross-sectional area in the range of about 1 to 900 sq. mm, preferably about 25 to 400 sq. mm, most preferably about 50 to about 100 sq. mm.

[0070] Figures 1A and 1B show prior art pan coated compositions having striations which are thus distinguishable from the present invention. Figure 1A is a micrographic cross-section of a prior art DRIXORAL 12 hour tablet (commercially available from Schering Plough Inc.) and Figure 1B is a micrographic cross-section of a prior art ADVIL tablet (commercially available from Wyeth Inc.). Both prior art products clearly have striations when viewed with a light microscope at magnifications ranging from about 50X to 400X.

[0071] The edible product of this invention may be made by a method comprising: (a) injecting a flowable, crystallizable carbohydrate into a mold cavity; (b) hardening the flowable, crystallizable carbohydrate into the edible product in the mold cavity; (c) removing the edible product from the mold cavity; (d) optionally drying the edible product; and (e) optionally finishing the surface of the edible product by smoothing or polishing. One embodiment of the method further comprises inducing thermal shock crystallization of the flowable crystallizable carbohydrate in the mold cavity to harden it in the mold cavity. Another embodiment of the method comprises cooling the flowable crystallizable carbohydrate below its glass transition temperature to form a non-flowable mass comprising an amorphous sugar-glass in the mold cavity.

[0072] As used herein, "flowable crystallizable carbohydrate" means a flowable mass comprising a crystallizable carbohydrate, for example carbohydrate crystals dispersed in a saturated carbohydrate solution, i.e., fondant or a molten carbohydrate in the form of an amorphous glass. As used herein, "hardening" means rendering the mass unflowable.

[0073] A preferred method for making the edible product of this invention in the form of a shell surrounding at least a portion of a core or substrate comprises: (a) injecting a heated, flowable, crystallizable carbohydrate into a mold cavity containing the substrate such that the flowable crystallizable carbohydrate surrounds a first portion of the substrate within the mold cavity; (b) rapidly changing the temperature of the mold cavity to induce thermal shock crystallization of the flowable crystallizable carbohydrate surrounding the first portion of the substrate; (c) opening the mold cavity and rotating the portion of the mold containing the substrate to expose a second portion of the substrate; (d) closing the mold cavity; (e) injecting heated, flowable, crystallizable carbohydrate into the mold cavity such that the flowable crystallizable carbohydrate surrounds the second portion of the substrate within the mold cavity; (f) rapidly changing the temperature of the mold cavity to induce thermal shock crystallization of the flowable crystallizable carbohydrate surrounding the second portion of the substrate; and (g) removing the coated substrate from the mold cavity.The flowable crystallizable carbohydrate may be heated in a heated feed tank.

[0074] In one particular embodiment, the shell comprises two parts that abut one another, thereby forming a shell that completely surrounds the substrate or core. Optionally, the shell may be dried, and optionally finished by smoothing or polishing in a rotating pan.

[0075] One suitable method for preparing the flowable crystallizable carbohydrate is to blend the crystallizable carbohydrate with sufficient water, and optionally to blend in a non-crystallizable carbohydrate, and optionally to cook the carbohydrate and water mixture, to obtain a desired solids content. In certain embodiments, further crystallizable carbohydrate may be added in crystalline form to the cooked carbohydrate and water mixture. Suitable temperatures for cooking the crystallizable carbohydrate range from about 100 to about 165°C. In certain embodiments, the crystallizable carbohydrate may be cooked to a temperature above its melting point, for example at temperatures from about 145 to about

165°C. In these embodiments, the flowable crystallizable carbohydrate is in the form of a glass. In certain other embodiments, the crystallizable carbohydrate may be cooked to a temperature below its melting point, for example at temperatures from about 100 to about 130°C. In these embodiments, the flowable crystallizable carbohydrate is in the form of a fondant.

[0076] In embodiments in which the crystallizable carbohydrate is combined with a non-crystallizable carbohydrate and cooked, the ratio of crystallizable carbohydrate to non-crystallizable carbohydrate may be from about 50:50 to about 90:10. In certain embodiments in which the flowable crystallizable carbohydrate is a glass, the ratio of crystallizable carbohydrate to non-crystallizable carbohydrate is preferably from about 50:50 to about 69:41. In certain other embodiments, in which the flowable crystallizable carbohydrate is a fondant, the ratio of crystallizable carbohydrate to non-crystallizable carbohydrate is preferably from about 70:30 to about 90:10. In these embodiments, the flowable crystallizable carbohydrate is preferably agitated during cooling.

[0077] In one particular embodiment, the flowable crystallizable carbohydrate is in the form of a metastable glass that will crystallize after about 1 to about 60 minutes upon cooling without agitation. In this embodiment, the ratio of crystallizable carbohydrate to non-crystallizable carbohydrate may be from about 65:35 to about 75:25. To induce the crystalizable carbohydrate to crystalize, additional crystallizable carbohydrate, in an amount up to about 1 percent by weight of the crystallizable carbohydrate, may be added in crystalline form to the cooked carbohydrate and water mixture.

[0078] Suitable temperatures for maintaining the heated flowable crystallizable carbohydrate at are from about 80 to about 98°C. Rapid temperature change of mold cavity is accordingly performed by quickly changing the temperature of the mold cavity from this

higher temperature range to a suitable "cold cycle" temperature for shock crystallizing the crystallizable carbohydrate. Suitable cold cycle temperatures range from about –10 to about 60°C, preferably from about –10 to about 25°C. Suitable mold temperatures for cooling the flowable crystallizable carbohydrate to below its glass transition temperature to form a non-flowable mass comprising an amorphous sugar-glass range from about 0 to about 80°C.

[0079] In one embodiment, the dosage form of this invention is a solid dosage form comprising at least one active ingredient and the edible product of this invention.

[0080] In another embodiment, the dosage form of this invention comprises at least one active ingredient, an edible shell made from the edible product of this invention, and a substrate which may be a core, with the edible shell residing on the substrate or surrounding at least a portion thereof. As used herein, the term "substrate" refers to a surface or underlying support upon which another material resides or acts, and the term "core" refers to a material such as a substrate which is enveloped or surrounded by some other material such as a shell. Any of the shell, core , substrate, or combination thereof may contain an active ingredient such as a pharmaceutically active ingredient.

[0081] In one embodiment, the edible shell covers at least a portion of the substrate. The substrate may be any edible material, and preferably may be selected from solid forms such as, for example, capsules, tablets, pills, lozenges, pellets, granules, powders, taffy, nougat, caramel, chocolate and the like; semi-solid forms such as for example gels, jellies, cremes, fondants, fudge, and the like; and liquid forms such as suspensions, solutions, syrups, emulsions, and the like.

[0082] In another embodiment, the substrate is a core which may be compressed or molded. The core may optionally be at least partially covered by a compressed, molded or sprayed sub-coating. In one preferred embodiment of this invention, the core is obtained by

compressing a powder. The powder may preferably comprise an active ingredient and optionally contain various excipients, such as binders, disintegrants, lubricants, fillers, glidants and the like, as is conventional, or other particulate material of a medicinal or non-medicinal nature, such as inactive placebo blends for tableting, confectionery blends, and the like. In one embodiment, the core comprises active ingredient, powdered wax (such as shellac wax, microcrystalline wax, polyethylene glycol, and the like), and optionally disintegrants and lubricants and is described in more detail at pages 4-11 of copending United States Patent Application Serial No.09/966,493, the disclosure of which is hereby incorporated by reference.

[0083] The core may be in a variety of different shapes. For example, in one embodiment the core may be in the shape of a truncated cone. In other embodiments the core may be shaped as a polyhedron, such as a cube, pyramid, prism, or the like; or may have the geometry of a space figure with some non-flat faces, such as a cone, cylinder, sphere, torus, or the like. Exemplary core shapes which may be employed include tablet shapes formed from compression tooling shapes described by "The Elizabeth Companies Tablet Design Training Manual," (Elizabeth Carbide Die Co., Inc., p.7 (McKeesport, Pa.) (incorporated herein by reference) as follows (the tablet shape corresponds inversely to the shape of the compression tooling):

1. Shallow Concave.
2. Standard Concave.
3. Deep Concave.
4. Extra Deep Concave.
5. Modified Ball Concave.
6. Standard Concave Bisect.
7. Standard Concave Double Bisect.
8. Standard Concave European Bisect.
9. Standard Concave Partial Bisect.
10. Double Radius.
11. Bevel & Concave.
12. Flat Plain.
13. Flat-Faced-Beveled Edge (F.F.B.E.).

14. F.F.B.E. Bisect.
15. F.F.B.E. Double Bisect.
16. Ring.
17. Dimple.
18. Ellipse.
19. Oval.
20. Capsule.
21. Rectangle.
22. Square.
23. Triangle.
24. Hexagon.
25. Pentagon.
26. Octagon.
27. Diamond.
28. Arrowhead.
29. Bullet.
30. Barrel.
31. Half Moon.
32. Shield.
33. Heart.
34. Almond.
35. House/Home Plate.
36. Parallelogram.
37. Trapezoid.
38. Figure 8/Bar Bell.
39. Bow Tie.
40. Uneven Triangle.

[0084] In another embodiment of the invention, the dosage forms of this invention comprise a core made from a blend of powders having an average particle size of about 50 to about 500 microns, e.g. about 100 to about 500 microns.

[0085] In another embodiment of the invention, the core is a directly compressed tablet, made from a powder which is substantially free of water soluble polymeric binders and hydrated polymers. This composition is advantageous for maintaining an immediate release dissolution profile, minimizing processing and material costs, and providing for optimal physical and chemical stability of the dosage form.

[0086] In a preferred embodiment, the core is prepared by the compression methods and apparatus described in copending U.S. Application Serial No. 09/966,509, pages 16-27, the disclosure of which is incorporated herein by reference. Specifically, the core is made

using a rotary compression module comprising a fill zone, insertion zone, compression zone, ejection zone, and purge zone in a single apparatus having a double row die construction as shown in Figure 6 of U.S. Application Serial No. 09/966,509. The dies of the compression module are preferably filled using the assistance of a vacuum, with filters located in or near each die. The purge zone of the compression module includes an optional powder recovery system to recover excess powder from the filters and return the powder to the dies.

[0087] The core may alternatively be made by the thermal setting molding method and apparatus described in copending U.S. patent application Serial No. 09/966,450, pages 57-63, the disclosure of which is incorporated herein by reference. In this embodiment, the core is formed by injecting a starting material in flowable form into a molding chamber. The starting material preferably comprises an active ingredient and a thermal setting material at a temperature above the melting point of the thermal setting material but below the decomposition temperature of the active ingredient. The starting material is cooled and solidifies in the molding chamber into a shaped core (i.e., having the shape of the mold).

[0088] According to this method, the starting material must be in flowable form. For example, it may comprise solid particles suspended in a molten matrix, for example a polymer matrix. The starting material may be completely molten or in the form of a paste. The starting material may comprise an active ingredient dissolved in a molten material. Alternatively, the starting material may be made by dissolving a solid in a solvent, which solvent is then evaporated from the starting material after it has been molded.

[0089] The core may also be made using the thermal cycle molding method and apparatus described in copending U.S. patent application Serial No. 09/966,497, pages 27-51, the disclosure of which is also incorporated herein by reference. In the thermal cycle molding method and apparatus of U.S. patent application Serial No. 09/966,497, a thermal cycle molding module having the general configuration shown in Figure 3 therein is

employed. The thermal cycle molding module 200 comprises a rotor 202 around which a plurality of mold units 204 are disposed. The thermal cycle molding module includes a reservoir 206 (see Figure 4) for holding flowable material to make the core. In addition, the thermal cycle molding module is provided with a temperature control system for rapidly heating and cooling the mold units. Figures 55 and 56 depict such a temperature control system 600.

[0090] In another embodiment of the invention, the core contains one or more inserts. The inserts can be made in any shape or size. For instance, irregularly shaped inserts can be made, that is shapes having no more than one axis of symmetry. Cylindrically shaped inserts may also be made. In a preferred embodiment, the insert is prepared by thermal setting molding using the method and apparatus described in copending U.S. patent application Serial No. 09/966,450, pages 57-63, as described herein. The starting material for the inserts may comprise any edible material which is desirable to incorporate into a shaped form, including active ingredients such as those active ingredients previously described with respect to the core, nutritionals, vitamins, minerals, flavors, sweeteners, and the like. Preferably, the starting material comprises an active ingredient and a thermal setting material. The thermal setting material may be any edible material that is flowable at a temperature between about 37 and about 120°C, and that is a solid at a temperature between about 0 and about 35°C. Preferred thermal setting materials include water-soluble polymers such as polyalkylene glycols, polyethylene oxides and derivatives, and sucrose esters; fats such as cocoa butter, hydrogenated vegetable oil such as palm kernel oil, cottonseed oil, sunflower oil, and soybean oil; mono- di- and triglycerides, phospholipids, waxes such as carnuba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; sugar in the form on an amorphous glass such as that used to make hard candy forms, sugar in a supersaturated solution such as that

used to make fondant forms; low-moisture polymer solutions such as mixtures of gelatin and other hydrocolloids at water contents up to about 30% such as those used to make "gummi" confection forms. In a particularly preferred embodiment, the thermal setting material is a water-soluble polymer such as polyethylene glycol.

[0091] In one embodiment of the invention, the insert may have an average diameter from about 100 to about 1000 microns. In another embodiment of this invention, the insert may have an average diameter or thickness from about 10% to about 90% of the diameter or thickness of the core. In yet another embodiment of this invention, the core may comprise a plurality of inserts.

[0092] The shell of the present invention may be formed by injection molding the edible product, advantageously minimizing or eliminating the need for direct-compression filler-binders such as microcrystalline cellulose, spray-dried lactose, mineral salts such as calcium phosphate, crystalline sugars such as sucrose, dextrates and the like. These materials would disadvantageously detract from the clarity and stability of the shell. Preferably the shell of the present invention comprises less than about 10%, e.g. less than about 1%, or less than about 0.1% of direct-compression filler-binders. The shell of the present invention is thus an improvement over compression-coated shells, which typically comprise at least about 30% of a direct-compression filler-binder, as described, for example, in WO 00/18447.

[0093] In a preferred embodiment of the invention, a shell is applied to a core in the form of a heated, flowable, crystallizable carbohydrate using the thermal cycle method and apparatus described in copending U.S. patent application Serial No. 09/966,497, pages 27-51 as described herein. In this embodiment, the heated, flowable, crystallizable carbohydrate is applied using a thermal cycle molding module having the general configuration shown in Figure 3 therein. The thermal cycle molding module 200 comprises a rotor 202 around which a plurality of mold units 204 are disposed. The thermal cycle molding module includes a

reservoir 206 (see Figure 4 therein) for holding the heated, flowable, crystallizable carbohydrate. In addition, the thermal cycle molding module is provided with a temperature control system for rapidly heating and cooling the mold units. Figures 55 and 56 depict the temperature control system 600.

[0094] The thermal cycle molding module is preferably of the type shown in Figure 28A of copending U.S. Application Serial No. 09/966,497, comprising a series of mold units 204. The mold units 204 in turn comprise upper mold assemblies 214, rotatable center mold assemblies 212 and lower mold assemblies 210 as shown in Figure 28C. Cores are continuously transferred to the mold assemblies, which then close over the cores. Crystallizable carbohydrate, which is heated to a flowable state in reservoir 206, is injected into the mold cavities created by the closed mold assemblies. The temperature of the flowable, crystallizable carbohydrate is then decreased, hardening it. The mold assemblies open and eject the coated cores. Coating is performed in two steps, each half of the cores being coated separately as shown in the flow diagram of Figure 28B of copending U.S. Application Serial No. 09/966,497 via rotation of the center mold assembly.

[0095] In one embodiment of the invention, only the substrate or core comprises one or more active ingredients. In another embodiment of this invention, only the shell comprises one or more active ingredients. In yet another embodiment of this invention, only the insert comprises one or more active ingredients. In yet another embodiment of this invention, both the core and shell comprise one or more active ingredients. In yet another embodiment of this invention, one or more of the core, the shell, or the insert comprises one or more of the active ingredients.

[0096] In another embodiment, the dosage form of this invention may further comprise a substrate or core having a composition different from that of the shell. In another embodiment, the shell material may also function as the substrate or core of the dosage form.

In another embodiment, the dosage form may further comprise a coating on the surface of the shell.

[0097] In another embodiment, the shell comprises a first shell portion and a second shell portion which are joined at an interface.

[0098] In another embodiment, the first and second shell portions are visually distinct from one another. For example the first and second shell portions may have a different size, shape, topography, or other geometric features, color, hue, opacity, and gloss.

[0099] In another embodiment, the dosage form of this invention is prepared by a method comprising providing a substrate and surrounding at least a portion of the substrate with an edible shell. The shell comprises at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the shell. At least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average size of less than about 100 microns, and the shell has a moisture content of not more than about 5% by weight loss on drying, preferably not more than about 3%, most preferably not more than about 1% by weight loss on drying. At least about 30%, preferably at least about 50%, most preferably at least about 80% of the cross-sectional area of the shell is non-striated, and the dosage form has a cross-sectional area in the range of about 1 to 900 sq. mm, preferably about 25 to 400 sq. mm.

[00100] This invention will be further illustrated by the following examples, which are not meant to limit the invention in any way.

Example 1

[0100] A batch of molded acetaminophen tablets were prepared according to the invention in the following manner:

[0101] A. Preparation of the Fondant (90% solids): Fondant sugar (Amerfond, available from Domino Foods) was placed in a thermostatically controlled planetary mixer bowl at room temperature fitted with a leaf blade and mixed slowly while adding water in the concentrations set forth in Table 1. Mixing was continued until the fondant was smooth and uniform.

Table 1

Ingredient	%	mg / tab	gms / batch
Amerfond	90.00	353.09	202.84
Purified Water USP	10.00	39.23	22.54
TOTAL	100.00	392.32	225.38

[0102] B. Preparation of the Bob Syrup: A 2-quart nonstick sauce pan and spatula were tared. Sucrose, corn syrup and water were added in the concentrations set forth in Table 2 and the gross weight was recorded. The mixture was cooked over a flame to 87% solids (about 115°C).

Table 2

Ingredient	%	mg / tab	gms / batch
Sucrose	81.00	989.85	568.64
Corn Syrup 42 D.E. (80%)	7.50	91.65	52.65
Purified Water	11.50	140.54	80.73
TOTAL	100.00	1222.04	702.02

[0103] C. Final Preparation: To the planetary mixing bowl containing the fondant (A), the invert sugar, water, and flavor was added in the concentrations set forth in Table 3 and mixed slowly until uniform. The bowl was covered with foil and heated to 90°C. The cooked "bob" syrup (B) was added and mixed in thoroughly. Acetaminophen was added and again mixed thoroughly until smooth and uniform. Small amounts of water were added to maintain a free flowing state.

Table 3

Ingredient	%	mg / tab	gms / batch
Fondant (90% solids)	17.77	392.32	225.38
"bob" (87 % solids)	55.34	1222.04	702.02
Acetaminophen	22.64	500.00	287.24
Purified Water	3.69	81.50	46.82
Invert Sugar	0.11	2.39	1.373
Sucralose	0.07	1.49	0.856
Flavor	0.38	8.50	4.883
TOTAL	100.00	2208.24	1268.57

[0104] The finished mixture was deposited into two-piece rubber or silicone molds at room temperature. Once the molds were filled, the mixture was allowed to harden sufficiently to be ejected from the molds. The product was allowed to dry thoroughly and harden further.

[0105] The molded cores were transferred to a coating pan and coated with a green colored shell for visual effect. Cross-sectional and side views of the molded dosage form having a molded core 20 and green-colored shell 22 are shown in Figs. 2A and 2B. In Figures 2A and 2B, the molded dosage form of Example 1 does not contain any striations.

Example 2

A batch of sugar coated solid dosage forms is made according to the invention. Table 4 below sets forth the fondant blend according to the invention used as the shell for the dosage forms:

Table 4

Ingredient	Trade Name	Supplier	Mg/tab	Theory Kg/batch
Fondant Sugar (90% solids)	Amerfond	Domino Sugar	196	83.40
Bob Syrup (87% solids)			611	260.00
Purified Water			42	17.87
Invert Sugar Solution (72% solids)			1	0.43
TOTAL			850	361.7

Dry fondant sugar is placed in a planetary mixer bowl and slowly blended using a leaf blade until smooth and uniform as 10% w/w purified water is added. Next the invert sugar solution and purified water is combined with the fondant and mixed thoroughly. Bob syrup, prepared by cooking a mixture of granulated sucrose, 42 DE corn syrup, and water (75:7:18 % w/w) to 87% solids or about 115°C, is added to the fondant /invert sugar mixture and blended until uniform (about 2 minutes).

[0106] The fondant blend is transferred to heated reservoirs. The reservoirs are described in copending U.S. Patent Application Serial No. 09/966,497, pages 27-51 and depicted as 206 in Figure 4 therein. The fondant blend is maintained within the reservoirs at 90-95°C and slowly stirred by means of a motorized mixing blade (not shown). The reservoirs are covered and pressurized to about 150 psi or sufficient pressure to allow the warm fondant blend to flow to a thermal cycle molding module as described in copending U.S. Application Serial No. 09/966,497.

[0107] Cores are prepared by the compression methods and apparatus described in copending U.S. Application Serial No. 09/966,509, pages 16-27, the disclosure of which is incorporated herein by reference. Specifically, the cores are made using a rotary compression module comprising a fill zone, insertion zone, compression zone, ejection zone, and purge zone in a single apparatus having a double row die construction as shown in Figure 6 of U.S. Application Serial No. 09/966,509. The dies of the compression module are preferably filled using the assistance of a vacuum, with filters located in or near each die. The purge zone of the compression module includes an optional powder recovery system to recover excess powder from the filters and return the powder to the dies. The cores are received by a transfer device having the structure shown as 300 in Figure 3 of copending U.S. Application Serial No. 09/966,414, the disclosure of which is incorporated by reference. The transfer device comprises a plurality of transfer units 304 attached in cantilever fashion to a belt 312 as

shown in Figures 68 and 69 of copending U.S. Application Serial No. 09/966,414. The transfer device rotates and operates in sync with the compression module and the thermal cycle molding module to which it is coupled. Transfer units 304 comprise retainers 330 for holding the cores as they travel around the transfer device.

[0108] The transfer device transfers the cores to the thermal cycle molding module, which applies the fondant blend to the cores. The thermal cycle molding module is of the type shown in Figure 28A of copending U.S. Application Serial No. 09/966,497. The mold units 204 of the thermal cycle molding module comprise upper mold assemblies 214, rotatable center mold assemblies 212 and lower mold assemblies 210 as shown in Figure 28C. Cores are continuously transferred to the mold assemblies, which then close over the cores. The mold assemblies are isothermally cooled to about 10°C. Then the heated, flowable fondant blend fills the mold assemblies. The fondant blend, a supersaturated sugar solution, is shock crystallized and sets as a firm solid mass surrounding the compressed cores. The mold assemblies open and eject the coated cores. Coating is performed in two steps, each half of the cores being coated separately as shown in the flow diagram of Figure 28B of copending U.S. Application Serial No. 09/966,497 via rotation of the center mold assembly.

[0109] Once the fondant blend is sufficiently set as a shell around the cores (i.e., 1-60 seconds), the mold assembly is opened and the in-process dosage form is ejected from the thermal cycle molding module and conveyed to a drier to thoroughly harden the shell and remove residual moisture, to obtain the finished dosage form.

[0110] Once dry, the coated cores may be optionally finished in a coating pan to provide added color, flavor, gloss, or smoothness.

Example 3

[0111] A batch of solid dosage forms is made according to the invention using the formulation set forth in Table 5 below:

Table 5

Ingredient	Trade Name	Supplier	Mg/tab	Theory Kg/batch
Fondant Sugar (90% solids)	Amerfond	Domino Sugar	196	83.40
Bob Syrup (87% solids)			611	260.00
Acetaminophen		Malincrodt	325	138.30
Purified Water			42	17.87
Invert Sugar Solution (72% solids)			1	0.43
TOTAL			1175	500.0

[0112] Dry fondant sugar is placed in a planetary mixer bowl and slowly blended using a leaf blade until smooth and uniform as 10% w/w purified water is added. Next the invert sugar solution and purified water is combined with the fondant and mixed thoroughly. Bob syrup, prepared by cooking a mixture of granulated sucrose, 42 DE corn syrup, and water (75:7:18 % w/w) to 87% solids or about 115°C, is added to the fondant / invert sugar mixture and blended until uniform (approximately 2 minutes). While maintaining this mixture at 90-95°C, acetaminophen is added and the mixture is uniformly blended.

[0113] The acetaminophen/fondant blend is transferred to heated reservoirs. The reservoirs are described in copending U.S. Patent Application Serial No. 09/966,497, pages 27-51 and depicted as 206 in Figure 4 therein. The acetaminophen/fondant blend is maintained within the reservoirs at 90-95°C and slowly stirred by means of a motorized mixing blade (not shown). The reservoirs 206 are covered and pressurized to about 150 psi or sufficient pressure to allow the acetaminophen/fondant blend to flow to a thermal cycle molding module having the specific configuration shown in Figure 26A of copending U.S. Application Serial No. 09/966,497. The thermal cycle molding module comprises center mold assemblies 212 and upper mold assemblies 214 as shown in Figure 26C, which mate to form mold cavities. As rotor 202 rotates, the opposing center and upper mold assemblies close. The mold assemblies are isothermally cooled to about 10°C. Acetaminophen/fondant

blend is injected into the mold cavities. As the acetaminophen/fondant blend fills the mold cavities, the supersaturated sugar solution is shock crystallized and sets as a firm solid mass containing suspended acetaminophen crystals. Once set (i.e., 1-60 seconds), the mold assemblies are opened and the finished dosage forms are ejected from the thermal cycle molding module and conveyed to a drier to thoroughly harden.

[0114] Once dry, the dosage forms are optionally finished in a coating pan to provide added color, flavor, gloss, or smoothness.

[0115] Although this invention has been illustrated by reference to specific embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made which clearly fall within the scope of this invention.

The invention claimed is:

1. An edible product comprising at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the product, wherein at least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less, the product has a moisture content of not more than about 5% by weight loss on drying, at least about 30% of the cross-sectional area of the product is non-striated, and the product has a cross-sectional area in the range of about 1 to 900 sq. mm.

2. The product of Claim 1 comprising about 60% of a crystallizable carbohydrate.

3. The product of Claim 2 comprising about 75% of a crystallizable carbohydrate.

4. The product of Claim 1, in which the crystals have an average particle size of less than about 50 microns.

5. The product of Claim 1 having a moisture content of not more than about 3% loss on drying.

6. The product of Claim 5 having a moisture content of not more than about 1% loss on drying.

7. The product of Claim 1, in which at least about 50% of the cross-sectional area of the product is non-striated.

8. The product of Claim 1, in which at least about 80% of the cross-sectional area is non-striated.

9. The product of Claim 1 comprising at least one active ingredient.

10. A method of making an edible product, comprising: (a) injecting a flowable, crystallizable carbohydrate into a mold cavity; (b) hardening the flowable, crystallizable carbohydrate into an edible product in the mold cavity; and (c) removing the edible product from the mold cavity.

11. An edible product prepared by a method comprising: (a) injecting a flowable, crystallizable carbohydrate into a mold cavity; (b) hardening the flowable crystallizable carbohydrate into an edible product in the mold cavity; and (c) removing the edible product from the mold cavity.

12. A dosage form comprising at least one active ingredient and an edible shell residing on at least a portion of a substrate, wherein the shell comprises at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the shell, at least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less, the shell has a moisture content of not more than about 5% by weight loss on drying, at least about 30% of the cross-sectional area of the shell is non-striated, and the dosage form has a cross-sectional area in the range of about 1 to 900 sq. mm.

13. The dosage form of Claim 12, in which the shell comprises a first portion and a second portion which are joined at an interface.

14. The dosage form of Claim 13, in which the first and second shell portions are visually distinct.

15. The dosage form of Claim 12, in which the substrate comprises an active ingredient.

16. The dosage form of Claim 12, in which the substrate is a core, and the edible shell surrounds the core.

17. The dosage form of Claim 12, in which the shell comprises an active ingredient.

18. The dosage form of Claim 16, in which the core comprises an active ingredient.

19. The dosage form of Claim 16, in which the shell and the core each comprise an active ingredient.

20. The dosage form of any of Claims 17-19, in which the active ingredient is capable of dissolution upon contacting of the dosage form with a liquid medium, and dissolution of the active ingredient meets USP specifications for immediate release tablets containing the active ingredient.

21. A dosage form prepared by a method comprising:

(a) providing a substrate;

(b) providing at least a portion of the substrate with an edible shell, wherein the shell comprises at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the shell, at least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less, the shell has a moisture content of not more than about 5% by weight loss on drying, at least about 30% of the cross-sectional area of the shell is non-striated, and the dosage form has a cross-sectional area in the range of about 1 to 900 sq. mm; and

(c) providing at least one active ingredient in the substrate or the shell or a combination thereof.

22. A method of preparing a dosage form comprising: (a) injecting a heated, flowable, crystallizable carbohydrate into a mold cavity containing a substrate such that the flowable crystallizable carbohydrate surrounds a first portion of the substrate within the mold cavity; (c) changing the temperature of the mold cavity to induce thermal shock crystallization of the flowable crystallizable carbohydrate surrounding a first portion of the substrate; (d) opening the mold cavity and rotating the portion of the mold containing the substrate to expose a second portion of the substrate; (e) closing the mold cavity; (f) injecting heated, flowable, crystallizable carbohydrate into the mold cavity such that the flowable crystallizable carbohydrate surrounds the second portion of the substrate within the mold cavity; (g) rapidly changing the temperature of the mold cavity to induce thermal shock crystallization of the flowable crystallizable carbohydrate surrounding the second portion of the substrate; and (h) removing the substrate from the mold cavity.

23. A dosage form comprising at least one active ingredient and at least about 50% by weight of a crystallizable carbohydrate based upon the weight of the dosage form, wherein at least about 90% by weight of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less, the dosage form has a moisture content of not more than about 5% by weight loss on drying, at least about 30% of the cross-sectional area of the dosage form is non-striated, and the dosage form has a cross-sectional area in the range of about 1 to 900 sq. mm.

24. The dosage form of Claim 23 comprising about 60% of a crystallizable carbohydrate.

25. The dosage form of Claim 24 comprising about 75% of a crystallizable carbohydrate.

26. The dosage form of Claim 23, in which the crystals have an average particle size of less than about 50 microns.

27. The dosage form of Claim 23 having a moisture content of not more than about 3% loss on drying.

28. The dosage form of Claim 26 having a moisture content of not more than about 1% loss on drying.

29. The dosage form of Claim 23, in which at least about 50% of the cross-sectional area of the dosage form is non-striated.

30. The dosage form of Claim 23, in which at least about 80% of the cross-sectional area of the dosage form is non-striated.

FIG. 1B PRIOR ART

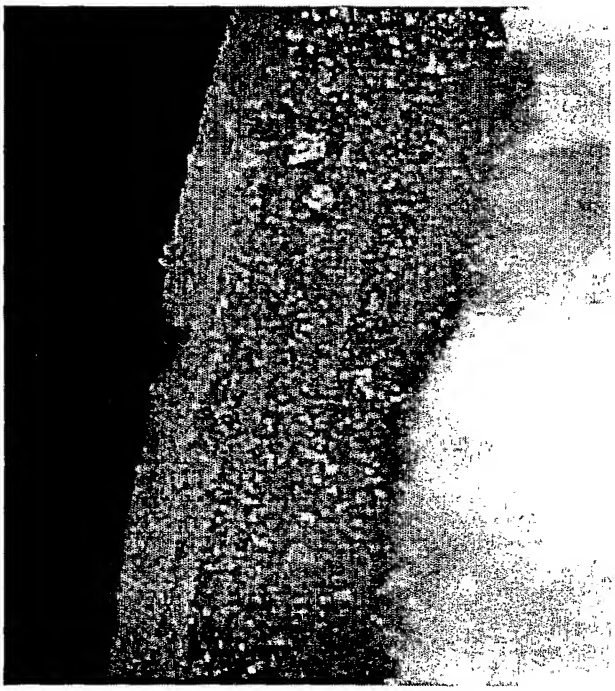


FIG. 1A PRIOR ART

FIG. 2A

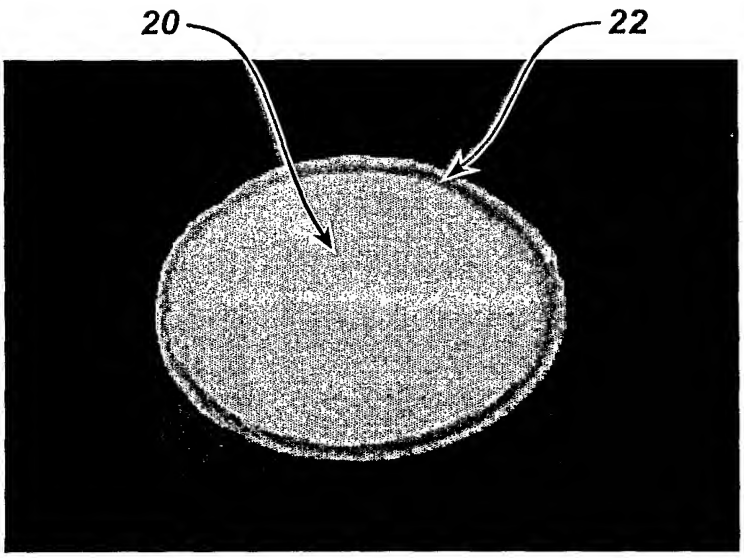
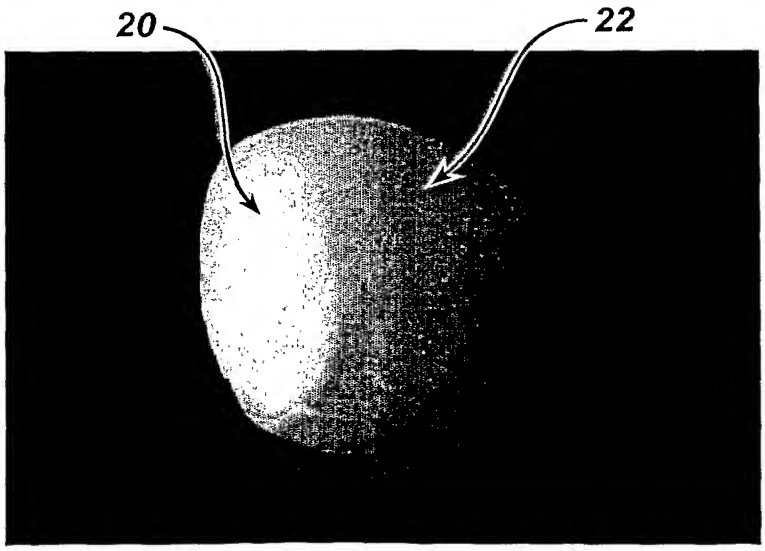


FIG. 2B



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/31164

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/20 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 273 793 A (FARIEL HARRY F ET AL) 16 June 1981 (1981-06-16) column 3, line 17-60 column 6, line 11-19 ---	1-3,5, 7-11, 23-25, 27,29,30
X	US 4 271 206 A (FARIEL HARRY F ET AL) 2 June 1981 (1981-06-02) column 3, line 11-50 column 4, line 43-66 column 6, line 16-32; claims 1-3,10,11 --- -/--	1-3,5, 7-11, 23-25, 27,29,30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2003	20/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Friederich, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/31164

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 871 781 A (MYERS GARRY L ET AL) 16 February 1999 (1999-02-16) column 4, line 29-34; examples; tables column 12, line 48-51	1,2,4-9, 23,24, 26-30
X	US 4 372 942 A (CIMILUCA PAUL A) 8 February 1983 (1983-02-08) column 2, line 35-37; examples	1-3,5, 7-9,12, 15-21, 23-25, 27,29,30
X	US 4 762 719 A (FORESTER MARK) 9 August 1988 (1988-08-09) table 1	1-3,5-9, 12, 15-19, 21, 23-25, 27-30
X	US 3 627 583 A (TROY JOHN P ET AL) 14 December 1971 (1971-12-14) example 6	1-9, 23-30
X	US 4 362 757 A (CHEN ANDY C C ET AL) 7 December 1982 (1982-12-07) column 4, line 21-25; examples; table 1	1-9

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-9,12-21,23-30 (partially)

Claims 1-9, 12-21 and 23-30 have been searched partially for the following reasons:

Present claims 9, 12-21 and 23-30 relate to an extremely large number of possible products ("active ingredient", "substrate"). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the products claimed ("pharmaceutically active ingredient", see the examples).

The parameter "at least about 30% (resp. 50 or 80%) of the cross-sectional area of the product (resp. the shell) is non-striated" in claims 1, 7, 8, 12, 21, 23, 29 and 30 is considered to lead to a lack of clarity within the meaning of Article 6 PCT.
This is also the case for the parameter "wherein at least about 90% of the crystallizable carbohydrate comprises crystals having an average particle size of about 100 microns or less" in claims 1-9, 12-21 and 23-30 since this parameter is usually not determined in a product obtained by a molding process.
It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the products prepared in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/31164

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-9,12-21,23-30 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/31164

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 4273793	A	16-06-1981	NONE		
US 4271206	A	02-06-1981	NONE		
US 5871781	A	16-02-1999	US	5622719 A	22-04-1997
			US	5597416 A	28-01-1997
			US	5518551 A	21-05-1996
			US	5866163 A	02-02-1999
			AT	221772 T	15-08-2002
			AU	700583 B2	07-01-1999
			AU	2818595 A	05-01-1996
			BR	9508034 A	16-09-1997
			DE	69527711 D1	12-09-2002
			DE	69527711 T2	05-12-2002
			EP	0764019 A1	26-03-1997
			HU	76550 A2	29-09-1997
			JP	10504282 T	28-04-1998
			NO	965388 A	13-02-1997
			WO	9534293 A1	21-12-1995
			US	5616344 A	01-04-1997
			US	5567439 A	22-10-1996
			US	5653926 A	05-08-1997
			US	5648033 A	15-07-1997
			US	5662849 A	02-09-1997
			US	5733577 A	31-03-1998
			US	5851552 A	22-12-1998
			US	5853762 A	29-12-1998
			US	5728400 A	17-03-1998
			US	5851553 A	22-12-1998
			US	6020002 A	01-02-2000
			AU	681431 B2	28-08-1997
			AU	7447994 A	27-04-1995
			CA	2131852 A1	08-04-1995
			CN	1104256 A ,B	28-06-1995
			EP	0656426 A2	07-06-1995
			JP	7184700 A	25-07-1995
			US	5935600 A	10-08-1999
			US	5965162 A	12-10-1999
			US	5895664 A	20-04-1999
			US	5587172 A	24-12-1996
			US	5593502 A	14-01-1997
			ZA	9407204 A	12-05-1995
			AU	688339 B2	12-03-1998
			AU	7157594 A	23-03-1995
			AU	7193498 A	24-09-1998
			CA	2131485 A1	11-03-1995
			CN	1107515 A ,B	30-08-1995
			EP	0646650 A2	05-04-1995
			IL	110826 A	01-06-2000
			IL	125916 A	06-12-2000
			JP	7148000 A	13-06-1995
			US	5601076 A	11-02-1997
			US	5827563 A	27-10-1998
US 4372942	A	08-02-1983	CA	1170491 A1	10-07-1984
US 4762719	A	09-08-1988	NONE		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/31164

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3627583 A	14-12-1971	CA 937167 A1	20-11-1973
		DE 2020982 A1	19-11-1970
		FR 2042385 A1	12-02-1971
		GB 1310925 A	21-03-1973
		IT 968013 B	20-03-1974
		JP 50013332 B	19-05-1975
		NL 7006008 A ,B	02-11-1970
US 4362757 A	07-12-1982	CA 1154627 A1	04-10-1983
		DE 3172919 D1	19-12-1985
		EP 0052413 A2	26-05-1982
		JP 1337632 C	29-09-1986
		JP 57138400 A	26-08-1982
		JP 60056477 B	10-12-1985